IOSR Journal of Dental and Medical Sciences (IOSR-JDMS)
e-ISSN: 2279-0853, p-ISSN: 2279-0861.Volume 23, Issue 3 Ser. 5 (March. 2024), PP 40-43
www.iosrjournals.org

Risk factors for WHO Group II ovulatory dysfunction among infertile women

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Abstract
Background
Infertility is a disease defined by the failure to achieve a clinical pregnancy even after 12 months or more of regular unprotected sexual intercourse. It affects 10-15 % of couples worldwide, 3.9 % in India and 11.1% in Kerala. WHO group II accounts for 85% of ovulatory dysfunction. Therefore we conducted this study to identify the potentially modifiable risk factors.
Methods
81 infertile women with menstrual irregularity and normal FSH value were selected as cases and 81 infertile women with regular cycles were selected as controls. Information was collected using Pre-structured questionnaire, food frequency and International physical activity questionnaire. Risk factors such as obesity, diet, physical activity, occupation, Socio economic status, birth weight and family history were studied. Data was entered into Excel sheet and analyzed using appropriate statistical test.
Results
Mean age among cases was 28.3years and mean age of controls was 30.1 years. Upper and middle class of socioeconomic status .BMI> 23 kg/m^2, Physical inactivity, animal protein intake more than once a week and Abdominal obesity were found to be risk factor for WHO group II ovulatory dysfunction. No association was found between birth weight, family history, occupation and age at menarche and WHO group II ovulatory dysfunction.
Conclusion
Upper and middle socioeconomic class, BMI >23 kg/m2, abdominal circumference >80 cm, physical inactivity and consumption of animal protein more than once a week are risk factors for WHO group II ovulatory dysfunction.

Date of Submission: 13-03-2024 Date of Acceptance: 23-03-2024

I. Introduction

World health organisation defines Infertility as a disease defined by the failure to achieve a clinical pregnancy even after 12 months or more of regular unprotected sexual intercourse.[1] Whereas sub fertility is used to describe women and couples who are not sterile but with decreased reproductive efficiency. 85-90% of women conceive within 1 year of marriage. Hence infertility affects 10-15 % of couples[2].Globally it is estimated that 60-80 million couples suffer from infertility every year, of which probably between 15-20 millions (25%) are in India alone[3]. WHO estimates of primary Infertility in India are 3.9 % (age-standardized to 25-49 yr) and 16.8 % (age-standardized to 15-49y yr) [4]. Infertility in Kerala is 11.1%, of which 9.1% is primary and 2% is secondary infertility[3]. Infertility resulting from ovulatory dysfunction account for about 21% or a fifth of all of infertility and 30% of female infertile patients[5].

The human reproductive process is complex, but for purposes of evaluation, is classified into:

1. Male factor: Sperm has to be deposited at or near the cervix at or near the time of ovulation, ascend into the fallopian tubes, and should have the capacity to fertilize the oocyte[2].
2. Ovarian factor: Ovulation of a mature oocyte should occur, ideally on a regular and predictable basis[2].
3. Cervical factor: The cervix should capture, filter, nurture, and release sperm into the uterus and fallopian tubes[2].
4. Uterine factor: The uterus must be receptive to embryo implantation and capable of supporting subsequent normal growth and development[2].
5. Tubal factor: The fallopian tubes have to capture ovulated ova and effectively transport sperm and embryos[2].

The ovulatory factor refers to the ability of a woman to normally undergo the process of ovulation, while the absolute proof of ovulation is pregnancy[5]. Hypothalamic-pituitary-ovarian (HPO) axis must works in concert to allow for the production of offspring by means of cyclic production of gonadotropic and steroid

hormones. This cycle is regulated tightly to select a dominant follicle for ovulation, meanwhile priming the endometrium for implantation. The ovary plays a very crucial role in the production of steroid hormone required for follicular development and maturation of oocyte. It contains a definite number of oocytes that a woman will have for the span of her reproductive life. It also influences the hormonal milieu required for oocyte maturation and fertilization. This complex regulation can be negatively impacted when pathologies occur within any juncture of the HPO axis[6].

Ovulatory dysfunction is identified on the basis of clinical history (irregular periods) or a midluteal progesterone level below the ovulatory threshold of 30 nmol/l[7]. WHO has classified ovulatory dysfunction into:
WHO Group I: Hypogonadotropic Hypogonadal Anovulation.
WHO Group-II: Eugonadotropic Euestrogenic Anovulation.
WHO Group-III: Hypergonadotropic Anovulation.[8]
WHO type II accounts for 85% of ovulatory dysfunction and predominantly involves women with polycystic ovaries[7].

Infertility is a life crisis with invisible losses, and grave consequences. Among different causes of infertility ovulatory dysfunction is most easily diagnosed and also most treatable cause.

II. Materials And Methods:

Ours is a Case control study conducted in SAT hospital, Thiruvananthapuram from July 2018 to June 2019. 81 cases and 81 controls between 20–45 yrs of age were taken. Case were infertile with Ovulatory dysfunction, menstrual irregularity[9,10], with normal FSH value[11]. Controls were infertile women with regular cycles. All data regarding age, age of menarche, type of infertility.

Occupation, Socioeconomic status, Birth weight, family history, BMI, Abdominal obesity, Physical activity (International physical activity questionnaire- short form), Diet (food frequency questionnaire) and Hormonal profile, were collected and analyzed to find out the risk factors for WHO group II ovulatory dysfunction. These data were entered into Excel sheet. Statistical tests of significance were used and analysis was done using appropriate statistical software. Odds ratio was calculated and significant odds were taken for conclusive analysis.

III. Results

Of the 81 cases 48.15% were only PCOS, no case of only hyperprolactinaemia, 9% were having only thyroid disease, 4.9% had PCOS and hyperprolactinaemia, 22.4% had PCOS and Thyroid disease, 2.4% had Hyperprolactinemia and Thyroid, 2.4% had PCOS, Hyperprolactinemia and thyroid disease and 11% did not fall into any category. Mean age among cases was 28.3years and mean age of controls was 30.1 years. It was noted that patients with WHO group II ovulatory were younger compared to controls. The distribution of primary and secondary infertility was similar among cases and controls. No significant difference was found in the occupation, age of menarche, Family history, birth weight among cases and controls.

Table no 1: Distribution of disease among cases.

Si. No.	Diagnosis	N	%
1	PCOS	39	48.15 %
2	Hyperprolactinemia	0	0 %
3	Thyroid disease	7	9%
4	PCOS + Hyperprolactinemia	4	4.9%
5	PCOS + Thyroid disease	18	22.4%
6	Hyperprolactinemia + Thyroid disease	2	2.45%
7	PCOS + Hyperprolactinemia + Thyroid disease	2	2.45%
8	Unclassified	9	11%

Upper and middle class of socioeconomic status, physical inactivity, animal protein intake and obesity was found to be a significant risk factor for WHO group II ovulatory dysfunction.

Table 2: Comparison of BMI categories among cases and controls.

BMI	Case	Control	odds
Under weight	5 (6.2%)	13 (16%)	
Normal	18 (22.2 %)	25 (30.9%)	1.87 (0.57-6.19)
Overweight/ obese	58 (71.6 %)	43 (53.1%)	3.50 (1.16-10.57)

$X^2 = 6.92$, P=0.03

We also found that abdominal obesity was a significant risk factor (odds ratio = 4.07, (χ^2 =18.18, p= <0.01), and risk increases from 3.23 to 4.83 as the abdominal circumference increases to more than 90 cm.

Table 3: Comparison of abdominal obesity among cases and controls.

Abdominal Circumference	Case	Control	Odds
< = 80 cm	31 (38.3 %)	58 (71.6 %)	
81 – 90 cm	19 (23.5 %)	11 (13.6 %)	3.23 (1.37-7.65)
>90 cm	31 (38.3 %)	12 (14.8 %)	4.83 (2.18-10.72)

X^2 = 18.72, P<0.01

Risk was seen to increase with increased frequency of animal protein intake, odds was 1.17 if taken more than once a week and 2.73 when taken on daily basis. Abdominal obesity (p= 0.00, OR=5.31) and daily intake of animal protein (p=0.03, OR=2.8) were also seen independent risk factor while normal BMI was found to be protective.

Table 4: Independent predictors of WHO group II ovulatory dysfunction.

		B	S.E.	P	Odds (95% CI)
Abdominal obesity (Absent ®)	Present	1.67	0.39	0.00	5.31 (2.45 - 11.51)
Animal protein (Rare ®)	>Once/week	0.11	0.48	0.82	1.12 (0.44 - 2.87)
	Every day	1.03	0.47	0.03	2.8 (1.11 - 7.04)
Physical activity (High active ®)	Inactive	0.82	0.63	0.19	2.28 (0.66 - 7.84)
	Minimally active	-0.17	0.63	0.79	0.85 (0.25 - 2.89)

IV. Discussion:

In present study BMI >23 was found to be a significant risk factor for WHO group II ovulatory dysfunction (χ^2 = 6.92, p = 0.03) with odds ratio of 3.50, while having normal BMI is protective and odds of not having the disease 1.87 in people with normal BMI. While according to Gulam Saidunnisa Begum et al only obese patients were at 1.74 times more risk of PCOS when compared to participants with normal BMI (p=0.030)[12]. Rich-Edwards et al found U-shaped association, with relative risks of ovulatory disorder infertility below a BMI of 20 and above a BMI of 24[13]. Chavarro et al also found a J-shaped relationship between BMI and ovulatory disorder infertility, wherein compared to women with normal BMI , those women with BMI between 25–29.9 and below 20 had a similarly higher risk of ovulatory disorder infertility, whereas those with BMI 30 and above had more than twofold greater risk[14].

Gulam Saidunnisa Begum et al found no association between risk of PCOS and abdominal obesity[12], but in our study we found significant association(p = <0.01), OR=4.02) and odds of having WHO group II ovulatory dysfunction among patients with abdominal circumference 81-90 cm was 3.23 which increases to 4.83 as the abdominal circumference increases to more than 90 cm.

N A Desai et al found higher percentage of PCOS girls belong to upper socioeconomic class (45.37%) when compared to non PCOS girls (35.43%)[15]. similarly in this study also we found that 69 % of the subjects with WHO group II ovulatory dysfunction belonged to upper and middle class compared to 46.9% of the control(p=0.036).

Gulam Saidunnisa Begum et al, concluded that participants with family history of PCOS carry a little higher risk [RR 1.07 (CI 0.709-1.619)] of development of PCOS compared to those without a family history[12.]Bao Shan et al also observed that bad mood (***OR*** = 2.852), family history of diabetes (***OR*** = 7.008), family history of infertility (***OR*** = 11.953), menstrual irregularity of mother (***OR*** = 2.557)were the risk factors of PCOS[16]. In another study by N A Desai, it was seen that most of PCOS girls were having family history of diabetes mellitus (37.81%), thyroid (20.16%) and hypertension (17.64%) as compared to normal girls (4.06%,

6.43%, 18.76% respectively)[15]. Like antiomo et al, we also failed to find any association between positive personal or family history and Eugonadotropic Euestrogenic Anovulation[17].

Gulam Saidunnisa Begum et al says that Participants consuming fast food diet for more than 3 days/ week have 1.7 times more risk of developing PCOS compared less than 3 days/week(p=0.044)[12]. In a prospective cohort study by Chavarro et al, increasing adherence to the "fertility diet" (high "fertility diet" score by a lower intake of trans fat with a simultaneous greater intake of monounsaturated fat, a lower intake of animal protein with greater vegetable protein intake, a higher intake of high-fiber, low-glycemic carbohydrates, greater preference for high-fat dairy products; higher nonheme iron intake; and higher frequency of multivitamin use) was associated with a lower risk of ovulatory disorder infertility (*P* for trend<.001) and also infertility due to other causes. Women in the highest quintile of the "fertility diet" score had a 66% (95% CI 52–77%) lower risk of ovulatory disorder infertility and a 27% (95% CI 5–43%) lower risk of infertility due to other causes. The association between the "fertility diet" score and ovulatory infertility was not modified by levels of age, parity, or BMI [14].It also said that Women who consumed iron supplements had a significantly lower risk of ovulatory infertility when compared to those women who donot (relative risk 0.60, 95% confidence interval 0.39–0.92)[14]. In our study we found that Animal protein intake was a risk factor. Consumption of animal protein on once a week had 1.17 odds of having WHO group II ovulatory dysfunction and on increasing ingestion to daily basis odds increased to 2.73. Other dietary factors were not found to be risk factors of group II ovulatory dysfunction.

Gulam Saidunnisa Begum et al could not establish physical inactivity as a risk factor[12] , but Bao shan et al says lack of physical exercise (***OR*** = 1.866) were the risk factors of PCOS[16]. According to Green et al found 8% of nulligravid women with ovulatory abnormalities exercised 60 minutes or more per day, as compared to 5 per cent of their controls (relative risk = 1.7). No such association was observed in secondary infertility. while according to Chavarro et al time spent in vigorous physical activities was unrelated to overall infertility and due to ovulatory disorders[18] .Rich-Edwards et al comments that each additional hour of vigorous exercise per week was associated with a 7% relative risk reduction in ovulatory disorder infertility. When examined specific vigorous activities separately, the largest reductions in relative risk were observed for running (34% reduction per hour per week) and jogging (22%), and smaller estimated relative risk reductions were observed for racquet sports (12%), lap swimming (5%), aerobics / calisthenics (5%), and biking (5%). There was no association seen between moderate-intensity activity and relative risk of ovulatory infertility[32]. In our study we found the odds of physically inactive people to have WHO group II ovulatory dysfunction is 1.63 compared to physically active. Minimal physical activity was seen to be protective (p=0.018, OR=0.62).

Melo et al in a study of 165 women from Brazil, has shown that women born small for gestational age are twice as likely to have PCOS than women born appropriate for gestational age[19]. In another study of 35 women from Italy, 19 of whom had been small for gestational age and the rest were premature, but with birth weight appropriate for gestational age, Low birth weight was found to be associated with clinical and biochemical markers of PCOS[20]. AG Shayeb et al fails to demonstrate a significant association between in utero factors represented primarily by birth weight and subsequently developing ovulatory dysfunction[21]. In our study because most of the subjects could not remember their birth weight, we fail to comment on this.

V. Conclusion

- Upper and middle socioeconomic class, BMI >23 kg/m2, abdominal circumference >80 cm, physical inactivity and consumption of animal protein more than once a week are risk factors for WHO group II ovulatory dysfunction.
- Abdominal obesity and daily intake of animal protein are independent risk factors for WHO group II ovulatory dysfunction.
- Normal BMI and Minimal physical activity are protective against WHO group II ovulatory dysfunction

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